REMARKS

Status of the Claims

Claims 1, 26-29, and 48-66 are pending in the application.

Claims 2-25 and 30-47 were previously cancelled.

Claims 61-62 are cancelled with entry of this amendment.

Claims 1, 26-29, 48-60 and 63-82 are currently under consideration with entry of this amendment.

Claims 67-82 are new.

Summary

Claims 1, 26-29 and 48-66 are pending in the application and were examined in the Office Action dated 23 February 2004. Applicants note with appreciation that the Office has withdrawn the rejection of claims 1 and 26-48 under 37 U.S.C. §112, first paragraph. However, the following new objections and claim rejections have been raised: **(a)** the drawings have been objected to under 37 C.F.R. §1.83(a) as failing to show every feature of the invention specified in the claims; **(b)** claim 61 has been objected to as informal; **(c)** claims 50 and 60-62 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement; **(d)** claims 1, 26-29, 48-53 and 63-66 stand rejected under 35 U.S.C. §103(a) as unpatentable over International Publication WO 97/38698 to Manning et al. ("Manning"); **(e)** claims 50-52 stand rejected under 35 U.S.C. §103(a) as unpatentable over Manning in view of U.S. Patent No. 4,472,394 to Peterson ("Peterson"); and **(f)** claims 54-59 stand rejected under 35 U.S.C. §103(a) as unpatentable over Manning. Applicants respectfully traverse all pending objections and claim rejections for the following reasons.

Overview of the Amendment

Applicants, by way of this amendment, have cancelled claims 61-62, submitted amendments to claims 1, 26-28, 48, 50, and 53-59 in order to place the application into condition for allowance or at least to place the claims in better form for appeal, and have

added new claims 67-82. More specifically, claims 61 and 62 have been cancelled without prejudice and disclaimer. Cancellation of these claims is not in acquiescence to any pending grounds of rejection, and applicants expressly reserve their right to bring the claims again in another related application.

Claim 1 has been amended to remove the volume and delivery quantity limitations inserted by way of the amendment dated 14 November 2003; to remove excess, repetitive and/or superfluous language in the preamble and body of the claim; and to more clearly recite that the drug unit is inserted directly and completely into the round window niche. Support for the amendments to claim 1 can be found throughout the specification and claims as originally filed, and in particular in the specification at: page 6, lines 28-32 (controlled release carrier materials); page 9, lines 17-24 (insertion directly into the round window niche); page 9, lines 28-31 (carrier material can be non-biodegradable); page 11, lines 1-4 (complete placement in the round window niche); page 12, lines 8-18 (placement in the round window niche, complete insertion); page 31, lines 13-29 (non-biodegradable carrier material); page 32, line 16 through page 33, line 22; and page 36, lines 16-21 (bioadhesive gels, hyaluronic acid and other non-synthetic polymers). Accordingly no new matter has been added by way of these amendments to claim 1, and the entry thereof is respectfully requested.

Claims 26-28 and 50 have merely been amended to recite the invention with greater particularity. For example, claim 26 has been amended to now expressly recite the volume limitation taken from claim 1. Support for this amendment can be found in previously submitted claim 1, and in the specification at page 42, line 3 through page 43, line 2. Claim 27 has been amended to now recite that the drug delivery unit is configured as a pellet, disk, tablet, plate, sphere, cube, cylindrical unit, strand, plug, paste, or amorphous mass. Support for this amendment can be found in the specification at page 12, lines 8-13; and at page 41, lines 23-35. Claim 28 has been amended to now expressly recite the delivery quantity limitation taken from claim 1. Support for this amendment can be found in previously submitted claim 1, and in the specification at page 8, lines 17-19; and page 10, lines 16-18. Claim 50 has been amended merely to remove language objected to by the Office. Applicants submit that no new matter has been added by way

of the amendments to claims 26-28 and 50, and the entry thereof is respectfully requested.

Claims 48 and 53-59 have been amended to merely remove excess, repetitive and/or superfluous language from the body of the claim (to remove "synthetic controlled release") necessitated by the amendments to claim 1. Accordingly no new matter has been added by way of the amendments to claims 48 and 53-59, and the entry thereof is respectfully requested.

New claims 67 and 68 have been added to recite the features that the carrier material is biodegradable or synthetic, respectively. Support for these new claims can be found throughout the specification and claims as originally filed, particularly in claim 1. In addition, support can be found in the specification at page 11, lines 18-35 (synthetic materials); and page 26, line 32 through page 28, line 34 (biodegradable materials). Claim 69 recites that the drug delivery unit comprises a soft, semi-soft, or pliable carrier material. Support for this feature can be found in the specification at page 23, lines 28-35.

New claim 70 recites that release of the therapeutic agent from the drug delivery unit is without inadvertent delivery to other tissue outside the round window niche. Support for this feature can be found in the specification at page 22, lines 1-7.

New claim 71 recites a method substantially identical to that of claim 1, wherein the drug delivery unit is configured as a pellet, disk, tablet, plate, sphere, cube, cylindrical unit, strand, plug, paste, or amorphous mass. Support for this new claim can be found throughout the specification and claims as originally filed, specifically in claim 1 and in the specification at page 12, lines 8-13; and at page 41, lines 23-35.

New claims 72-82 correspond to an earlier series of dependent claims in the application (a series of claims that depend directly or indirectly from claim 1). More particularly, new claim 72-74 correspond to pending claims 50-52, new claim 75 corresponds to pending claim 53; new claims 76 and 77 correspond with new claims 67 and 68, and recite the features that the carrier material is biodegradable or synthetic, respectively. Support for these new claims can be found throughout the specification and claims as originally filed, particularly in claim 1. New claim 78 corresponds with

pending claim 66, new claim 79 corresponds with pending claim 69, and new claims 80-82 correspond with pending claims 63-65, respectfully.

Applicants respectfully submit that new claims 67-82 are adequately supported by the specification and claims of the application as originally filed, and therefore no new matter has been added by way of these new claims. Entry of new claims 67-82 is respectfully requested.

The Objections under 37 C.F.R. §1.83(a)

The drawings have been objected to under 37 C.F.R. §1.83(a) as failing to show every feature of the invention specified in the claims. More particularly, the Office objects that the multi-phased composite drug delivery unit of claim 60 must be shown in the figures, or the feature cancelled from the claim. In response, applicants draw the Office's attention to Figure 2, and the accompanying disclosure from the specification at page 40, lines 6-30. As can be seen, the multi-phase carrier material (14) is shown in Figure 2 and described in detail in the specification. Reconsideration and withdrawal of the objection to claim 60 is thus respectfully requested.

In addition, the Office has objected that recited features from claims 61 and 62 are missing from the figures. In response, applicants note that claims 61 and 62 have been cancelled by the present amendment to the claims, rendering the objection moot.

The Objection to the Claims

Claim 61 was objected to as informal on the basis that double punctuation at the end of the claim. Correction was required. Claim 61 has been cancelled by this amendment, and the objection is thus moot.

The Rejections under 35 U.S.C. §112, First Paragraph

Claims 50 and 60-62 stand rejected under 35 U.S.C. §112, first paragraph, on the basis of written description. In particular, the Office has objected that the range from claim 50 of "at least 24 hours" does not find basis in the specification. In response, applicants draw the Office's attention to the amendment to claim 50 tendered herewith,

wherein the range has been amended to now recite "over a period of 24 hours." Support for this limitation can be found in the specification at page 35, lines 5-9 ("over a 24-hour period or longer"). Reconsideration and withdrawal of the rejection of claim 50 under 35 U.S.C. §112, first paragraph, is thus respectfully requested.

The Office has further objected that the subject matter of claims 60-62 lack sufficient disclosure. No specific basis for these rejections was provided. Applicants thus assume that the present claim rejections are grounded on the same basis as the earlier objections to the drawings. Accordingly, with regard to claim 60, applicants respectfully traverse the rejection. With respect to the recited multi-phase composite drug unit recited in claim 60, applicants again draw the Office's attention to Figure 2, and the accompanying disclosure from the specification at page 40, lines 6-30. As can be seen, the multi-phase carrier material (14) is shown in Figure 2 and described in detail in the specification. Reconsideration and withdrawal of the rejection of claim 60 under 35 U.S.C. §112, first paragraph, is thus respectfully requested.

Finally, claims 61 and 62 have been cancelled by the present amendment, rendering the rejection of those claims moot.

The Rejections under 35 U.S.C. §103

Claims 1, 26-29, 48-53 and 63-66 stand rejected under 35 U.S.C. §103(a) as unpatentable over Manning. This is a new ground of rejection. More particularly, the Office asserts that Manning "discloses the invention substantially as claimed, [that is,] a drug delivery unit comprised of a biocompatible, biodegradable polymer support and at least one pharmacologically active agent that is placed such that it substantially contacts the round membrane of the middle ear." Office Action at page 3. The Office goes to assert "this would encompass being in direct contact or against and at least partially in said round window niche" and that the Manning device "provides extended release." Office Action at page 4. The Office then concludes that applicants' claims are obvious over the Manning reference. Applicants respectfully disagree.

Initially, applicants note that as a result of the present claim amendments, there are now two basic claim series, the first including independent claim 1 and all claims

dependent thereon (claims 26-29, 48-60, and 63-70), and the second including independent claim 71, and claims 72-82 that depend therefrom. The scope of applicants' claimed invention is thus summarized as either: (a) delivery of a therapeutic agent to the inner ear, where a drug delivery unit comprising a carrier material and the agent is inserted directly into the round window niche and positioned completely within the niche (see amended claim 1); or (b) delivery of a therapeutic agent to the inner ear, where a drug delivery unit comprising a carrier material and the agent is inserted directly into the round window niche so that it is either partially or completely within the niche, and where the drug delivery unit is in a non-liquid form (see new claim 71). Applicants submit that both of these claim series is patentably distinct from Manning for the following reasons.

The standard of patentability to be applied in obviousness rejections was set forth by the Supreme Court in *Graham v. John Deere*, 148 USPQ 456 (USSC 1966). In short, there are four factual inquiries that are used as a background for determining obviousness, that is, (a) one must determine the scope and contents of the prior art; (b) then ascertain the differences between the prior art and the claims in issue; (c) resolve the level of ordinary skill in the pertinent art; and (e) evaluate evidence of secondary consideration. Applying these inquiries to Manning, one sees that applicants' recited invention is patentable over that reference.

Initially, the problem to be addressed is how one can deliver a therapeutic to the inner ear. The inner ear lies behind the ear drum and is sealed off from the rest of the ear (e.g., the middle ear) by solid tissue or at least a membrane (like the round window membrane). The entire ear organ is in turn isolated from the rest of the body by the blood/labyrinthine barrier, a barrier that effectively prevents systemically applied therapeutics from reaching the inner ear unless an excessively large dose of medicine is given. Accordingly, with regard to the scope and content of the prior art, the vast majority of medical practitioners use either large dose systemic approaches (which can cause significant side-effects), or employ a very crude, blunt force method where the ear is lavaged or irrigated with a large volume of liquid therapeutic while the subject lies on his/her side. When the subject stands up or moves, the liquid will drain out of the ear

ending the delivery event. The other approach is that of Manning, where an improvement to the standard methods entails administration of a liquid ("the composition is always somewhat fluid", Manning, page 10, lines 21-22) through a needle ("the composition is fluid enough to be injected through a fine gauge needle as small as 26 gauge", Manning, page 5, lines 24-26) or a pumping device (see Manning, page 5, lines 21-23) into the middle ear, where the liquid was comprised of a therapeutic within an HA polymer system. Manning teaches that the middle ear accommodates volumes up to 0.8 ml (see Manning, page 9, line 26). Manning teaches that 0.2 ml of the liquid therapeutic is administered (see Manning, page 9, lines 23-26), thus, fully one quarter of the entire middle ear is flooded with the liquid. Manning goes on to teach that the liquid that has been administered must contact the round window membrane for subsequent delivery into the inner ear. Manning hopes to accomplish this in much the same way as the other approaches, where administration of enough liquid will ensure that some actually enters the round window niche where it can then contact the membrane. In this regard, applicants note that the volume of the round window niche is diminishingly small with respect to the rest of the middle ear, at least an order of magnitude smaller the 0.2 ml volume of liquid that Manning injects, so the majority of the therapeutic administered by Manning will not be contained within the round window niche, nor will it contact the round window membrane.

Although Manning is an improvement over the other methods available to the skilled artisan, it still has a number of problems. Significantly, the round window niche of the ear is specifically designed to remove foreign matter from the middle ear and away from the inner ear. Thus, the round window niche is covered with a mucous membrane and configured to drain under gravity, thereby sweeping material from the niche, which can then be removed from the ear by the ciliary action of cells lining the middle ear. What this means is that the majority of Manning's 0.2 ml dose of therapeutic does not get delivered, rather it drains out of the subject's ear just as the other methods do. Manning inherently recognizes this, and notes that at least 50% of the active agent is delivered within 4 hours and upwards of 90% of the active agent is delivered within 24 hours of administration, despite the possibility of the HA polymer to remain for up to 7 days (see

Manning, page 10, lines 1-10). This means that for a round of therapy that requires 7-10 days of continued delivery, the Manning method would have to be practiced up to 7-10 times.

Accordingly, the scope and contents of the prior art encompass only low efficiency systemic delivery methods, and relatively low-efficiency flooding methods using a liquid medicament. This scope and content is distinctly different from the scope and content of applicants' claims. This is because applicants' claims require that the drug delivery unit is inserted directly into the round window niche, and completely within the niche (see claim 1 *et seq.*), or alternatively that the drug delivery unit is not a liquid and is placed directly into the round window niche and positioned either partially or completely therein (see claim 71, *et seq.*). Accordingly, applicants' claims are manifestly different from Manning and the rest of the cited prior art. Applicants' claimed methods are further a significant improvement over the art, where now a therapeutic can be very specifically inserted directly into the target niche, avoiding potential inadvertent delivery to other tissue (important if ototoxic compositions are used), and ensuring direct delivery through the round window membrane for the duration of the controlled delivery event (hours, days, or even months).

With regard to the level of skill in the relevant art, applicants note that Manning likely represents a highly skilled artisan, whereas the ordinarily skilled artisan would usually resort to systemic medications or irrigation/lavage methods. However, there clearly has been a long-felt need for an improved method, as evidenced by Manning's activities, and prior methods (again Manning's) have failed to meet this need to a large extent. These secondary considerations are powerful evidence that applicants' claims are non-obvious and patentable over the cited art including Manning.

Accordingly, when the Graham inquiries are properly applied to applicants' recited methods, it is clear that Manning does not render those methods obvious. For all of the foregoing reasons, then, applicants submit that the rejection of claims 1, 26-29, 48-53 and 63-66 under 35 U.S.C. §103(a) over Manning is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited. In addition, applicants submit that

all of the pending claims as now amended likewise distinguish over Manning. Thus allowance of claims 1, 26-29, 48-60 and 63-82 is both proper and fair.

Claims 50-52 stand rejected under 35 U.S.C. §103(a) as unpatentable over Manning in view of Peterson. The Office applies Manning substantially as discussed above, and uses Peterson as a secondary reference to teach implantation of a controlled release composition beneath the ear of a domestic farm animal. Office Action at page 5. Applicants respectfully disagree.

As discussed above, the primary reference to Manning fails to teach or suggest all of the critical limitations of applicants' recited claims. The addition of Peterson's implants (of a systemically acting material—Peterson did not want the animal's ears to grow, he wanted weight gain) adds nothing to the Manning reference that would result in applicants' recited methods of direct administration into the round window niche. Applicant's agents are applied locally (directly though the round window niche into the inner ear) where they act locally. The combination of Peterson with Manning is thus both artificial and improper. For these reasons, applicants respectfully submit that the rejection of claims 50-52 under 35 U.S.C. §103(a) over Manning and Peterson is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited. In addition, applicants submit that all of the pending claims as now amended likewise distinguish over the combination of Manning and Peterson. Thus allowance of claims 1, 26-29, 48-60 and 63-82 is both proper and fair.

Finally, claims 54-59 stand rejected under 35 U.S.C. §103(a) as unpatentable over Manning. In particular, the Office asserts "Manning teaches the invention substantially as claimed" but acknowledges "Manning does not teach the material to be polyanhydride, polyorthoester, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydrophilic microsphere or bioadhesive material." Office Action at page 6. However, the Office nonetheless concludes that modification of the polymer material was "a mere design choice." Applicants respectfully traverse the rejection.

Again as discussed above, when properly considered Manning fails to render applicants' recited methods obvious. Accordingly, a mere design choice over a non-obvious method is still non-obvious. Applicants thus submit that the rejection of claims

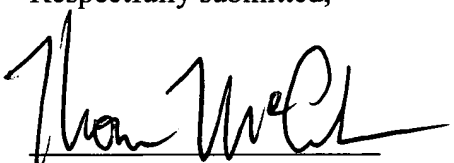
54-59 under 35 U.S.C. §103(a) over Manning is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited. In addition, applicants submit that all of the pending claims as now amended likewise distinguish over Manning. Thus allowance of claims 1, 26-29, 48-60 and 63-82 is both proper and fair.

CONCLUSION

Applicants submit that the pending claims define an invention that is both novel and nonobvious over the cited art, and thus all claims are in condition for allowance. Acknowledgement of this by the Office in the form of an early allowance is thus respectfully requested. In addition, if the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned at (408) 777-4915.

The appropriate fee is attached or authorized. If the Commissioner determines that an additional fee is necessary, the Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. **50-1953.**

Respectfully submitted,



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